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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,955	02/27/2004	Uri Galili	047940-0167	5776

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,955	GALILI ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 11/22/06 is acknowledged.

Claims 28- 50 are pending.

Claims 28-50 read on a method of inducing at least a partial immune tolerance to a carbohydrate antigen are under consideration in the instant application.

In view of the amendment, filed 11/22/06 the following rejections remain:

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 28-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing partial immune tolerance to carbohydrate antigens in mice, comprising administered an engineered population of white blood cells, that expressed α-gal epitope does not reasonably provide **enablement** for a method of inducing immune tolerance to any carbohydrate antigen in any mammals including human, comprising administering an engineered population of white blood cells that express said carbohydrate antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action, mailed on 08/23/06.

Applicant's arguments, filed 11/22/06 have been fully considered, but have not been found convincing

Applicant asserts that : (i) The inventors demonstrated the enablement of the invention, by showing the induction of immune tolerance to another carbohydrate antigen, B blood group antigen, as evidence by Declaration by Dr. Galili; (ii) The data from KO mouse model can be correlated to other mammals including human; (iii) Carbohydrate antigens of the present invention can be expressed on other mammalian cells, testing in monkeys is not necessary to establish the relevance of the method.

Contrary to Applicant's assertion, the issue raised in the previous Office Action was not about ability of one skill in the art to express on the surface of human cells.

As has been stated previously, the specification only discloses *in vivo* studies on KO mice. In said experimental model, an immune tolerance to carbohydrate antigen has been induced when engineered lymphocytes transduced with adenovirus containing α 1,3 GT gene have been administered. Administration of such lymphocytes into KO mice results in tolerization of naïve and memory anti-Gal B cells (see entire document, Examples 1 in particular). Similarly , in Declaration by Dr. Galili, it has been only shown that mice, administered with nucleofected lymphocyte expressing blood group B antigen, did not develop anti-B antibodies.
However, it is the Examiner position that said data does not support the enablement for the claimed method of inducing at least partial immune tolerance to any carbohydrate antigen in any mammals including human, comprising administering an engineered population of white blood cells that express said carbohydrate antigen.

The specification does not adequately teach how to effectively induce immune tolerance to any antigen in any mammals, by administering an engineered population of white blood cells that express any antigen. Moreover, no animals were used as model system to effectively induce immune tolerance to any carbohydrate antigen. Since there is no animal model studies and data in the specification to show the effectively of inducing immune tolerance to any carbohydrate antigen in any mammal, including human by administering an engineered population of white blood cell, it is unpredictable how to correlate limited results on KO mice with intended *in vivo* use. Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Mestas et al (J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans. Moreover, Ogawa et al., (Gene Therapy, 2004, Vol.11, pages 292-301) teach that KO mice lack a-gal epitope and thus not immunotolerant. **The relevance of this model and method for induction of tolerance to α–gal epitopes in human has first bé tested** in monkeys in order to determine whether this phenomenon (induction of tolerance to carbohydrate antigen), which is observed in

mice , is also applicable to primates (see entire document, page 299, right column in particular). In addition, in second publication, Ogawa et al., (Blood, 2003, Vol.101, pages 2318-2320) teach that carbohydrate antigens on glycoprotein differ from peptide antigens in that they cannot activate T cells directly because of their protrusion from MHC groove. (see entire document, page 2318 in particular).
Moreover, the induction of tolerance has been called the "Holy Grail" of transplantation, and like the grail itself, tolerance induction has remained an elusive goal (Schroeder et al., J. Surg. Res. 2003, 111:109:119, see entire document particularly the abstract and page 117). For example, in type I diabetes Pozzilli et al. demonstrate that while the induction of tolerance would be expected, it simply does not occur (see Pozzilli et al., Diabetologia 2000, 43:1000-1004). Other unsuccessful examples of tolerance induction in humans are known in the art. *Marketletter* (9/13/99) teaches the complete failure of tolerance induction in human trials. Wekerly et al (IDS) teach that it is possible to actively induce transplantation tolerance in mice even before the first successful renal transplantation in humans has been performed, but **clinical tolerance induction remains an elusive goal to the present day** (emphases added).

Thus, it is the examiner position that it is not clear that the skilled artisan could predict the efficacy of a method of inducing at least partial immune tolerance to any carbohydrate antigen in any mamma, including humans comprising administering engineered population of white blood cells that expressed said antigen.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed a method of inducing at least partial immune tolerance to any carbohydrate antigen in any mammals comprising administering engineered population of white blood cells that expressed said antigen in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 28-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bracy et al (Blood, 2000, V.96, pages 3008-3015) in view of US Patent 2002/0119571 and US Patent 5,879,675 for the same reasons set forth in the previous Office Action, mailed on 08/23/06.

Applicant's arguments, filed 11/22/06 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) neither US Patent 571 nor US Patent'675 teach or suggest inducing immune tolerance in mammal to carbohydrate antigen by expressing the carbohydrate antigen on white blood cells and administering them to the mammal; (ii) US Patent'675 only teaches a method which generally enhance the immune response, not to induce tolerance, thus cited references alone or in combination do not teach or suggest expression of carbohydrate antigen on white blood cell for the purposes of inducing immune tolerance to that antigen, (iii) Bracy et al., do not teach transduction via a replication defective adenovirus to express a carbohydrate antigen.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

Bracy et al., teach a method of inducing immune tolerance to carbohydrate antigen, comprising administering to a mammal engineered BM cells (see entire document, Abstract in particular). Said engineered BN cells have been constructed by inserting a nucleic acid encoding α-gal epitope using retroviral gene therapy (see entire document, Abstyract in particular). Bracy et al., teach suppressing T cell help response for successful induction of immune tolerance to carbohydrate antigen (see page 3013 in particular). Bracy et al., teach that if possible to achieve even a relatively low but detectable level of α -Gal expressing cells in primates it is likely to be able to eliminate B cells making α -Gal reactive antibodies (see page 3014 in particular).

Bracy et al., do not explicitly teaches a method of inducing immune tolerance comprising administering engineered population of lymphocytes, wherein said lymphocytes are transduced with replication defective adenovirus to express α -Gal epitope on its surface.

US Patent '571 teaches a method of inducing immune tolerance to an antigen in mammal, comprising administering to said animals engineered population of lymphocytes. (see entire document, Abstract and column 4 and 5 in particular). US Patent '571 teaches that said engineered lymphocytes are obtained by inserting a nucleic acid encoding the portion of the antigen (see column 4 in particular). US Patent '571 teaches the use of retrovirus gene transfer to obtained engineered lymphocytes (see column 4 in particular).

US Patent '675 teaches a method of engineering a population of cells expressing α-gal epitope on its surface, comprising transducing said cells with replication defective adenovirus containing α 1,3 GT gene. (see entire document, columns 8 and 10 in particular). US Patent '675 teaches that said engineered cells can be used to target immune response in mammals.

With regards to Applicant's comments that US Patent'675 only teaches a method which generally enhance the immune response, not to induce tolerance. It is noted that said reference has been used to demonstrate that at the time the invention was made one skill in the art would know how to express the carbohydrate antigen on the surface of human cells.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '571 and US Patent 675 to those of Bracy et al., to obtain a claimed method of inducing immune tolerance comprising administering engineered population of lymphocytes, wherein said lymphocytes are transduced with replication defective adenovirus to express α -Gal epitope on its surface.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because base on combine teaching of US Patent '571 and US Patent 675 it would be obvious to engineered a population of lymphocytes that would express α-gal epitope on its surface using replication defective adenovirus. Said engineered population of lymphocytes can be used instead of engineered population of BM cells to induced immune tolerance to

carbohydrate antigen as taught by Bracy et al. It is noted that Bracy et al., do not limited their studies to use only engineered BM cells. As has been discussed supra, Bracy et al., teach that if possible to achieve even a relatively low but detectable level of α -Gal expressing cells in primates it is likely that it will be possible to eliminate B cells making α -Gal reactive antibodies. One skill in the art would immediately recognized that induction of tolerance to a α -Gal epitope is not a characteristic limited to BM cells but is a more general phenomenon that can be induced by other cell, for example lymphocytes.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The following new ground of rejection are necessitated by the amendment filed 11/22/06

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is indefinite and ambiguous in the recitation of " protein antigen". There is insufficient antecedent basis for this limitation in the claims, since base Claim 28 does not recite "protein antigen".

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 29, 30, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

" wherein the expressed carbohydrate antigen does not activate T cells" claimed in claim 29, "wherein the carbohydrate antigen comprises a blood group antigen" claim in claim 30; suppressing the immune response of the mammal concurrently with (a), claimed in claim 43; removing substantially all cells that react with protein antigen from the mammal prior to (a), claimed in claim 44 represent a departure from the specification and the claims as originally filed. The passages pointed by the applicant do not provide a clear support for " wherein the expressed carbohydrate antigen does not activate T cells" claimed in claim 29, "wherein the carbohydrate antigen comprises a blood group antigen" claim in claim 30; suppressing the immune response of the mammal concurrently with (a), claimed in claim 43; removing substantially all cells that react with protein antigen from the mammal prior to (a), claimed in claim 44.

The specification and the claims as originally field only support for : (i) Blood group A or B antigens or the α gal epitope do not activate T cells for claims 29 and 30 ; (ii) suppressing T cell response of the mammal concurrently with (a), for claim 43.

10. No claim is allowed

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

1/17/07